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Healthcare utilization and costs in ARDS survivors: a 1-year longitudinal national US multicenter study

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Abstract

Purpose: To evaluate (1) post-discharge healthcare utilization and estimated costs in ARDS survivors, and (2) the association between patient and intensive care-related variables, and 6-month patient status, with subsequent hospitalization and costs.

Methods: Longitudinal cohort study enrolling from four ARDSNet trials in 44 US hospitals. Healthcare utilization was collected via structured interviews at 6 and 12 months post-ARDS, and hospital costs estimated via the Medical Expenditure Panel Survey. Adjusted odds ratios for hospitalization and adjusted relative medians for hospital costs were calculated using marginal two-part regression models.

Results: Of 859 consenting survivors, 839 (98%) reported healthcare utilization, with 52% female and a mean age of 49 years old. Over 12 months, 339 (40%) patients reported at least one post-discharge hospitalization, with median estimated hospital costs of US$18,756 (interquartile range $7852–46,174; 90th percentile $101,500). Of 16 patient baseline and ICU variables evaluated, only cardiovascular comorbidity and length of stay were associated with hospitalization, and sepsis was associated with hospital costs. At 6-month assessment, better patient-reported physical activity and quality of life status were associated with fewer hospitalizations and lower hospital costs during subsequent follow-up, and worse psychiatric symptoms were associated with increased hospitalizations.

Conclusions: This multicenter longitudinal study found that 40% of ARDS survivors reported at least one post-discharge hospitalization during 12-month follow-up. Few patient- or ICU-related variables were associated with

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Take-home message: In this national, multicenter prospective longitudinal study of ARDS survivors, 339 (40%) patients reported at least one hospitalization within 1 year and median estimated post-discharge hospital costs of US$18,756 (interquartile range $7852–46,174; 90th percentile $101,500), with 85/339 (25%) patients hospitalized within 30 days of discharge. Better patient-reported physical activity and quality of life measures at 6-month follow-up were consistently associated with both fewer subsequent hospitalizations and lower costs in the following 6 months, while worse psychiatric symptoms were associated with increased hospitalizations.

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hospitalization; however, physical, psychiatric, and quality of life measures at 6-month follow-up were associated with subsequent hospitalization. Interventions to reduce post-ARDS morbidity may be important to improve patient outcomes and reduce healthcare utilization.

Keywords: Patient readmission, Healthcare, Cost, Quality of life, Critical illness

Introduction

Survivors of critical illness, such as acute respiratory distress syndrome (ARDS), commonly experience long-term morbidity after hospital discharge, including physical, cognitive, and mental health impairments [1–7]. Previous ARDS studies demonstrate that hospitalization in the year post-ARDS is common [7–9]. However, the timing, risk factors, and associated costs for these post-discharge hospitalizations are not well understood, and most existing studies are single-centered with modest samples sizes [10]. Hence, using a national, multicenter cohort of 839 ARDS survivors from four randomized trials conducted by the National Heart, Lung and Blood Institute's ARDS Network (ARDSNet), we evaluated the longitudinal association of patient baseline and ICU-related exposures with post-discharge hospitalizations and associated healthcare costs during 1-year follow-up. In addition, we evaluated the association of patient-reported measures of physical function, psychiatric symptoms, cognitive function, and quality of life (QOL) at 6 months post-ARDS with subsequent 6- to 12-month hospitalizations and associated healthcare costs.

Methods

Study cohort

This analysis was conducted as part of the ARDS Network Long-Term Outcomes Study (ALTOS), which prospectively followed survivors from four national, multicenter randomized controlled trials (RCTs): ALTA trial (nebulized albuterol vs. placebo), EDEN (early versus delayed enteral nutrition), OMEGA (nutritional supplements vs. placebo), and SAILS (rosuvastatin versus placebo) [11–14]. We pooled patients from the intervention and control groups of these RCTs on the basis that the trials have similar enrollment criteria and no significant effects of the interventions on patients' short- or long-term outcomes [11–18]. Consecutive, mechanically ventilated ARDS patients were enrolled from November 2006 to September 2013. Patients were enrolled across 44 hospitals within 48 h of ARDS onset and 72 h of initiation of mechanical ventilation. ARDSNet exclusion criteria have been reported previously [11–14] and included severe comorbid malnutrition or lung, liver, or neuromuscular diseases; or limitations in life support at time of eligibility. For prospective follow-up at 6 and 12 months post-ARDS via the ALTOS study, survivors of these four ARDSNet trials were excluded, on an a priori basis, if they had preexisting cognitive impairment prior to admission (ascertained via medical records and/or patient/proxy report) or were non-English-speaking, homeless, or less than 18 years old. Across all participating intensive care units (ICU), these participants were managed with simplified versions of lung-protective mechanical ventilation and fluid conservative hemodynamic management protocols, with blood glucose control aimed at 80–150 mg/dL (tighter glucose control was permitted). The institutional review boards of all participating hospitals approved this study. Informed consent was obtained from patient or a proxy.

Baseline patient- and ICU-related exposures

Baseline patient-related exposures included age, gender, race (White vs. non-White based on patient/family report), estimated household income (based on zip code), healthcare insurance status (i.e., private insurance, Medicare, Medicaid, dual-eligibility for Medicare and Medicaid, or no coverage), obesity (body mass index (BMI) at least 30 kg/m^2), and the following comorbidities: diabetes mellitus, chronic pulmonary disease, or cardiovascular disease. ICU-related exposures included Acute Physiology and Chronic Health Evaluation (APACHE) III severity of illness score, ARDS risk factor (sepsis vs. all others), performance of tracheotomy during ICU stay, and ICU length of stay (LOS).

Exposures collected 6 months post-ARDS included (1) physical function, evaluated via the Functional Performance Inventory Short Form (FPI) (total score, and the physical exercise, maintaining house, and body care subscales scores) [19]; (2) psychiatric symptoms, evaluated via the Hospital Anxiety and Depression Scale (HADS) [continuous and binary (at least 8) scores for anxiety and for depression symptoms] [20], and the Impact of Event Scale-Revised (IES-R) [continuous and binary (at least 1.6) scores for post-traumatic stress disorder (PTSD) symptoms] [21]; (3) cognitive function, evaluated via the Mini-Mental Status Exam (MMSE) [22], [continuous and binary (less than 24)] scores for abnormal cognition); and (4) QOL, evaluated via the EQ-5D visual analogue scale (VAS) and utility score [23], and the Short Form-36 version 2 Health Survey (SF-36v2) physical and mental component scores (PCS and MCS, respectively) [24]; and (5) healthcare insurance status. Continuous variables were rescaled by previously

reported estimated minimally important difference (MID) (i.e., EQ-5D utility score, SF-36v2 PCS and MCS, and HADS subscales) [25–27]; or by half their standard deviation (SD) if the MID data have not been clearly established (i.e., FPI, MMSE, IES-R, and EQ-5D VAS) as per existing recommendations [28].

Outcome measures: post-discharge healthcare utilization and estimated costs over 1-year follow-up

Data on healthcare utilization were self-reported via structured interviews at 6- and 12-month follow-up. The data collection instrument was adapted from previous studies [2, 29, 30], and included inpatient admission type (hospitalization, skilled nursing facility, or rehabilitation facility), admission and discharge dates, and admission category for hospitalizations, and outpatient healthcare utilization. The healthcare utilization interviews were conducted using a detailed six-page case report form focused on healthcare utilization. Patients were asked questions about each individual type of healthcare utilization and queried about "landmark" personal events, such as birthdays and holidays, to improve temporal recall of events, as done in other surveys [31]. If patients had difficulty with recall, proxy respondents assisted in data reporting.

We evaluated direct medical costs of healthcare utilization from the payer perspective (Fig. 1) [10]. Using the Medical Expenditure Panel Survey (MEPS), a nationally representative healthcare utilization and cost database [32], we calculated the estimated costs associated with post-discharge healthcare utilization (additional detail in electronic supplementary material). All costs are reported in 2014 US dollars.

Statistical analysis

Patient baseline and ICU-related exposures were compared between patients with vs. without any hospitalization over 12-month follow-up using Chi-squared tests (categorical variables) and two-sample *t* tests (continuous variables). Hospitalization, rather than all healthcare utilization, was selected for analysis to facilitate comparability to international healthcare systems given that access to skilled nursing and rehabilitation facilities can vary across countries. Notably, the study outcome data had the following characteristics: (1) the binary presence vs. absence of a hospitalization in each 6-month time frame; and (2) among those with any hospitalization, a positively skewed cost distribution. Consequently, we evaluated each exposure variable's association with hospital costs using a marginal longitudinal two-part regression model [29, 33]. We built a two-part "base model" that includes a main effect of time (12- vs. 6-month follow-up), and relevant covariates based on prior related research [29, 33], in both the logistic model for presence vs. absence of a hospitalization and the linear model for the logarithm of cost among those hospitalized. In addition, we evaluated the association between patient status at 6-month follow-up with hospitalizations and estimated hospital costs incurred during the subsequent 6- to 12-month follow-up period using a marginal two-part regression model. To avoid overfitting this regression model, we individually added each 6-month exposure variable to our multivariable "base model" as previously described.

To evaluate the association of patient and ICU-related exposures with the time to first hospitalization, we used the Fine and Grey proportional subdistribution hazard regression model incorporating death as a competing risk [34]. In order to avoid overfitting the model, we created a base model with age, gender, race, estimated household income, and baseline healthcare coverage and then added other covariates individually to the model. This analysis was performed separately for time to first hospitalization within 30 days, and within 12 months, after hospital discharge.

For each regression model, we verified the linearity of each continuous exposure variable with the study outcomes by examining locally weighted scatterplot smoothing (LOWESS) of residuals from the regression model. In the multivariable models, multi-collinearity was evaluated using variance inflation factors. The Hosmer–Lemeshow test confirmed model fit in logistic regressions models. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX), and SAS 9.4 (SAS Institute, Cary, NC; NLMIXED procedure with 10 quadrature points).

Results

Patient characteristics and healthcare utilization

Of 859 consenting ARDS survivors, 839 (98%) reported healthcare utilization at 6- and/or 12-month follow-up (Fig. 2). The vast majority of survivors [97% (812/839)] were living at home pre-ARDS. Comparing baseline patient and ICU-related exposures between patients with ($n = 339$, 40%) vs. without ($n = 500$, 60%) any hospitalization during 12-month follow-up, patients with any hospitalization were relatively older, more likely to have healthcare insurance, and to have diabetes mellitus and cardiovascular disease at baseline (Table 1).

During 12-month follow-up, these 839 patients had a median [interquartile range (IQR)] of 1 (1–2) hospitalization, with 8 (3–20) days in hospital (Table 2), with 210 (30%) of these hospital admissions being for pneumonia or other infection (eTable 1). Of the 339 patients hospitalized, 94 (28%) had an ICU stay, with median (IQR) ICU LOS of 6 (3–13) days, with 47 (50%) of these 94 ICU

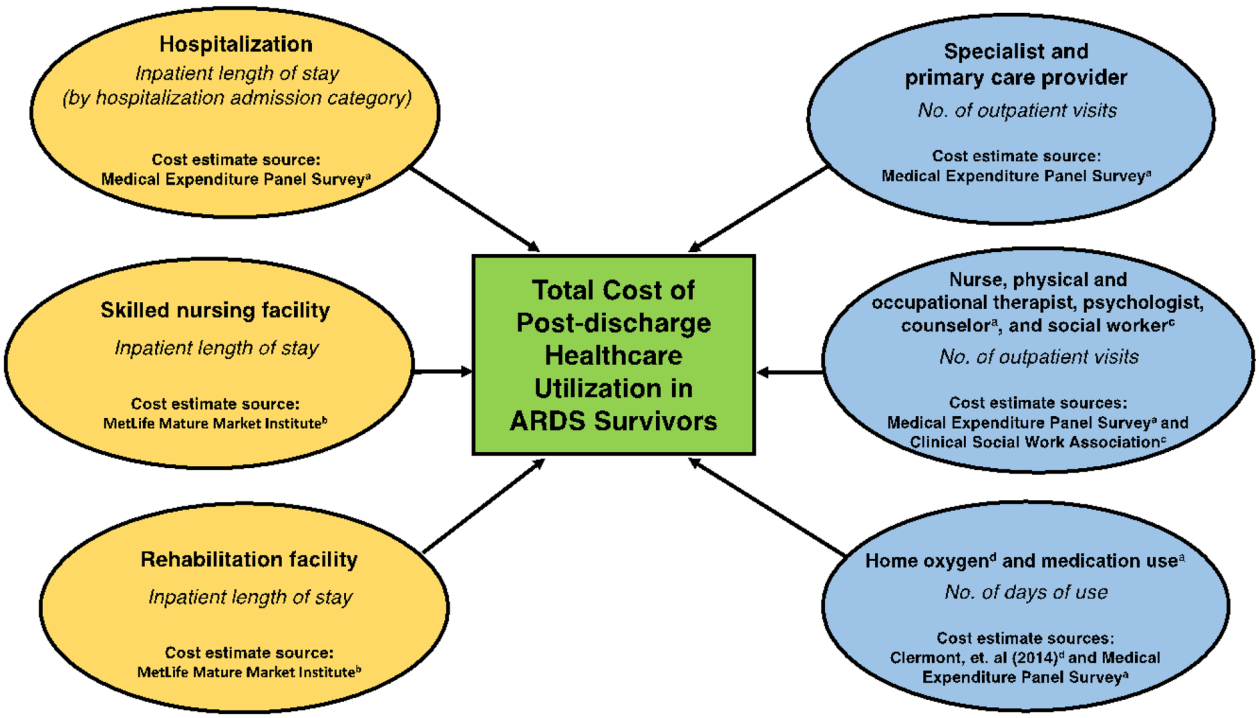

Fig. 1 Costing of post-discharge healthcare utilization in ARDS survivors. *ARDS* acute respiratory distress syndrome. No. number. [a]Agency for Healthcare Research and Quality (AHRQ), Medical Expenditure Panel Survey. Accessed on 1 Aug 2016. Available from https://meps.ahrq.gov/mepsweb/. [b]Metlife Mature Market Institute. Market survey of long-term care costs. Accessed on 10 Sept 2016. Available from https://www.metlife.com/assets/cao/mmi/publications/studies/2012/studies/mmi-2012-market-survey-long-term-care-costs.pdf. [c]Clinical Social Work Association. Accessed on 10 Sept 2016. Available from http://www.clinicalsocialworkassociation.org/Medicare. [d]Clermont G, Kong L, Weissfeld LA, Lave JR, Rubenfeld GD, Roberts MS, Connors AF Jr, Bernard GR, Thompson BT, Wheeler AP, Angus DC, Network NACT (2011) The effect of pulmonary artery catheter use on costs and long-term outcomes of acute lung injury. PLoS One 6:e22512

patients requiring mechanical ventilation for 8 (3–14) days (eTable 2). A total of 4% (32/815) and 3% (21/764) of patients reported requiring renal dialysis at 6- and 12-month follow-up, respectively. The incidence of new dialysis requirements in survivors not receiving dialysis prior to ARDS was 3% (23/815) and 2% (12/764), respectively. A total of 100 (12%) and 171 (20%) patients had at least one skilled nursing facility and rehabilitation facility stay, respectively, with total stays of 50 (23–134) and 20 (10–30) days, respectively. The vast majority (88%) of nursing and rehabilitation facility stays occurred during the initial 6-month follow-up period (eFigure 1). The median (IQR) cost for follow-up for all inpatient care (e.g., hospitalizations, skilled nursing facility, and rehabilitation facility stay) was $16,800 ($6200–41,300) with 81% attributable to post-discharge hospitalization (Table 2).

Outpatient Utilization and Costs

During the 12-month follow-up, 739 (88%) ARDS survivors visited a primary care provider and 716 (85%) visited at least one specialist physician, with pulmonology, cardiology, and psychiatry being the most frequently visited subspecialty physicians (eTables 4 and 5). The median (IQR) total outpatient cost was $6761 ($3590–12,037). The number of patients who required outpatient services from a physical therapist or occupational therapist was 382 (46%) and 162 (19%), respectively, while 148 (18%) visited a psychiatrist and 393 (48%) used psychiatric medication(s). Physical therapy and psychiatric visits were the two most costly outpatient categories (eTable 4).

Baseline patient- and ICU-related exposures associated with 1-year hospitalization and costs

Cardiovascular comorbidity (odds ratio (OR) and 95% confidence interval (CI) 1.39, 1.00–1.92, $P = 0.049$) and ICU LOS (1.10, 1.01–1.19, per week, $P = 0.023$) were associated with hospitalization after discharge, while sepsis (as an ARDS risk factor) was associated with 60% higher costs of hospitalization after discharge (relative median and 95% CI 1.60, 1.15–2.22, $P = 0.005$). Patient age, gender, race, estimated household income, and healthcare coverage were not independently associated with hospitalization or costs.

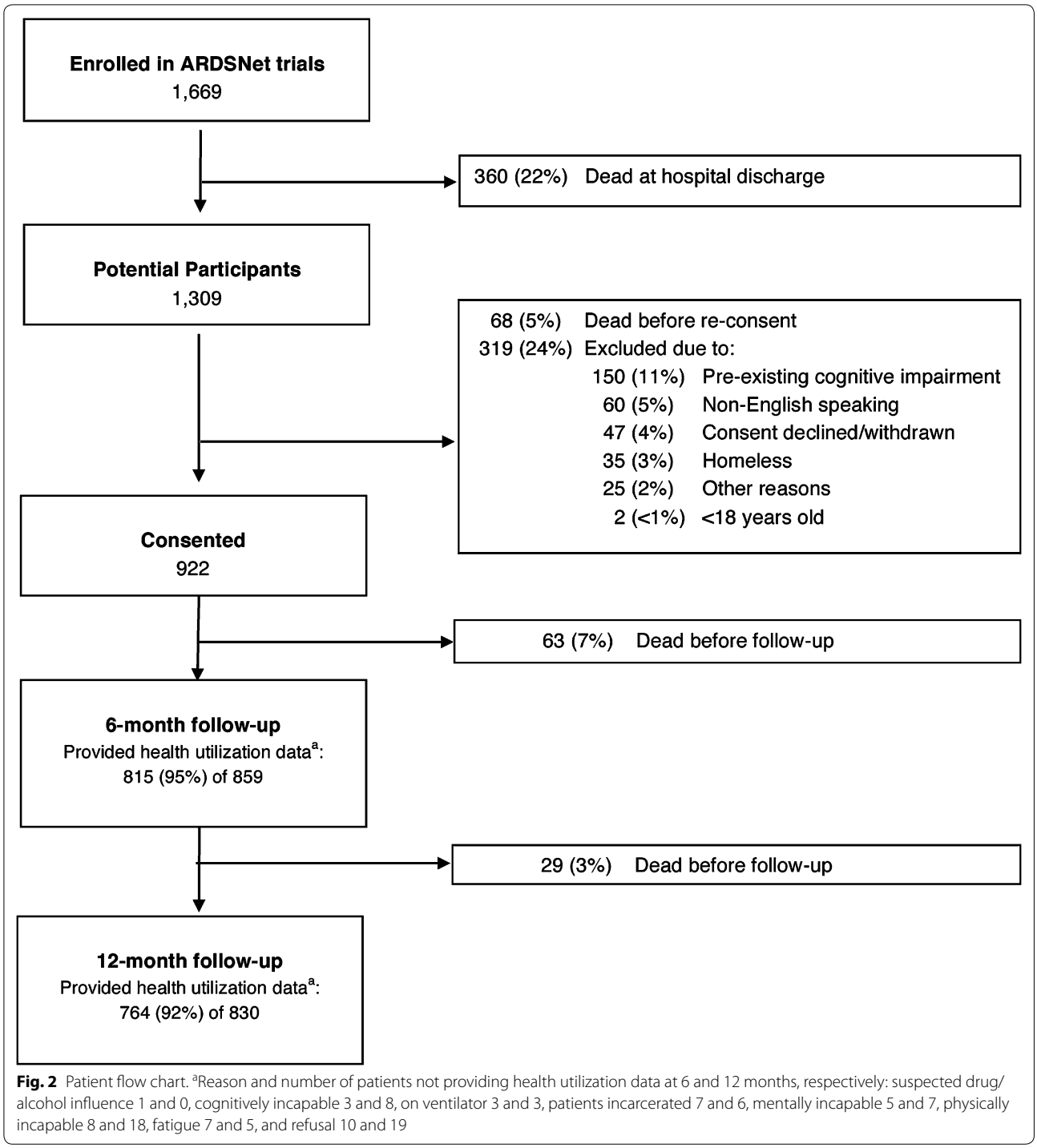

Fig. 2 Patient flow chart. [a]Reason and number of patients not providing health utilization data at 6 and 12 months, respectively: suspected drug/alcohol influence 1 and 0, cognitively incapable 3 and 8, on ventilator 3 and 3, patients incarcerated 7 and 6, mentally incapable 5 and 7, physically incapable 8 and 18, fatigue 7 and 5, and refusal 10 and 19

6-month patient status associated with 6- to 12-month hospitalization and costs

Better physical function and QOL measures at 6-month assessment were consistently associated with decreased hospitalization and hospital costs in the subsequent 6-month follow-up period (Table 4). For example, an improvement in self-reported overall physical functioning (i.e., a 0.5 SD increase in FPI total score) was associated with lower odds of hospitalization (OR and 95% CI 0.81, 0.72–0.90, $P < 0.001$) and 17% lower hospital costs (relative median and 95% CI 0.83, 0.76–0.90, $P < 0.001$). Symptoms of depression and anxiety, but not PTSD

Table 1 Patient characteristics, by hospitalization status

Variables	Total ($n = 839$)		Patients with any hospitalization ($n = 339$)		Patients with no hospitalization ($n = 500$)		P[a]
Patient baseline data							
Age, year, mean (SD)	49	(15)	51	(14)	48	(15)	**0.009**
Female, no. (%)	439	(52)	191	(56)	248	(50)	0.055
White, no. (%)	669	(80)	276	(81)	393	(79)	0.319
Estimated income[b], mean (SD), $10,000	5.1	(1.9)	5.1	(1.9)	5.2	(2.0)	0.469
Healthcare insurance[c], no. (%)	576	(85)	242	(89)	334	(82)	**0.020**
Insurance type[c,d], no. (%)							0.056
Private insurance	241	(36)	90	(33)	151	(37)	
Medicare	182	(27)	82	(30)	100	(25)	
Medicaid	95	(14)	43	(16)	52	(13)	
Dual Medicare and Medicaid	58	(9)	27	(10)	31	(8)	
No insurance	101	(15)	30	(11)	71	(18)	
Obesity[c,e], no. (%)	395	(47)	161	(48)	234	(47)	0.833
Diabetes mellitus, no. (%)	198	(24)	100	(30)	98	(20)	**0.001**
Cardiovascular disease[f], no. (%)	385	(46)	178	(53)	207	(41)	**0.002**
Chronic pulmonary disease[g], no. (%)	102	(12)	49	(14)	53	(11)	0.094
ICU-related baseline data[h,i]							
APACHE III score[c], mean (SD)	86	(26)	88	(28)	85	(25)	0.150
Sepsis as ARDS risk factor, No. (%)	664	(79)	270	(80)	394	(79)	0.767
Tracheostomy in ICU, no. (%)	111	(13)	51	(15)	60	(12)	0.202
ICU length of stay (days)[c], mean (SD)	14	(16)	16	(22)	14	(10)	0.059

SD standard deviation, *no.* number, *APACHE* Acute Physiology and Chronic Health Evaluation, *ARDS* acute respiratory distress syndrome, *ICU* intensive care unit

Bold values represent statistical significance $P < 0.05$

[a] *P* value calculated by two-sample *t* test or Chi-squared test

[b] Estimated household income is based on zip code of residence

[c] Variables with missing data (*n*, %): healthcare insurance status (162, 19%), obesity (2, <1%), APACHE III (25, 3%), ICU length of stay (6, 1%)

[d] Column percentages may not add to 100% due to rounding

[e] Obesity defined as body mass index (BMI) ≥30 kg/m^2

[f] Cardiovascular disease comorbidity was defined as having at least one of the following: hypertension, prior myocardial infarction, chronic heart failure, peripheral vascular disease, or prior stroke

[g] Less common comorbidities include (%) immune suppression (8), arthritis (6), peptic ulcer disease (4), cirrhosis (3), leukemia (2), hemodialysis (2), acquired immunodeficiency syndrome (AIDS) (2), solid tumor with metastasis (1), non-Hodgkin's lymphoma (1), hepatic failure (0), dementia (0)

[h] A total of 19% (162/839) of patients were documented to have had acute renal failure or received renal replacement therapy during the first 7 days in the ICU

[i] The vast majority [96% (803/839)] of ALTOS patients were discharged from their study site hospital without receiving mechanical ventilation

symptoms, were positively associated with hospitalization. Better cognitive function (as measured by MMSE score) was associated with 7% lower hospital costs (0.93, 0.86–0.99, per 0.9 unit, $P = 0.035$).

Timing of first hospitalization

A total of 85 (25%) of the 339 patients ever hospitalized during 12-month follow-up, or 10% of the entire 839-patient cohort, had a hospital readmission within 30 days after discharge, with a median (IQR) time to hospitalization of 10 (3–17) days and the most common admission category (20% of readmitted patients) being pneumonia. Higher median estimated household income was associated with earlier hospitalization, with adjusted hazard ratio (HR; 95% CI) of 1.12 (1.02–1.22, $P = 0.013$) per $10,000 increase in estimated income (eTable 6).

Among the 339 patients ever readmitted to the hospital over the 12-month follow-up, the median (IQR) time to readmission was 101 (25–219) days. ICU LOS was independently associated with a shorter time to readmission (adjusted HR (95% CI) 1.04 (1.02–1.05), $P < 0.001$, per week) (eTable 7).

Discussion

In this national, multicenter, longitudinal study of 839 ARDS survivors, 40% were hospitalized over 12-month follow-up, with 25% of those readmitted within 30 days after discharge from their index ARDS hospitalization. ARDS survivors who were hospitalized had a median (IQR) of 8

Table 2 Hospital, skilled nursing, and rehabilitation facility data during 12-month follow-up after acute respiratory distress syndrome

	Discharge to 6 months ($n = 815$)[a]	6 to 12 months ($n = 764$)[a]	Total 1 year ($n = 839$)[a]
Hospital			
Patients using service[b], no. (%)	220 (27)	177 (23)	339 (40)
No. admissions, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)
Length of stay[c], days, median (IQR)	7 (3–19)	6 (3–14)	8 (3–20)
Cost per patient, $, median (IQR)	15,600 (5900–46,000)	15,400 (7900–31,200)	18,800 (7900–46,000)
Total cohort cost, $ (%)	8,914,000 (61)	5,732,000 (39)	14,645,600 (100)
Skilled nursing facility stay			
Patients using service[b], no. (%)	94 (12)	19 (2)	100 (12)
No. of admissions, median (IQR)	1 (1–1)	1 (1–1)	1 (1–2)
Length of stay[c], days, median (IQR)	45 (21–126)	60 (30–142)	50 (23–134)
Cost per patient, $ median (IQR)	8700 (4100–24,400)	11,600 (5800–27,500)	9700 (4400–26,000)
Total cohort cost, $ (%)	1,529,600 (81)	364,300 (19)	1,894,000 (100)
Rehabilitation facility stay			
Patients using service[b], no. (%)	159 (20)	18 (2)	171 (20)
No. of admissions, median (IQR)	1 (1–1)	1 (1–1)	1 (1–1)
Length of stay[c], days, median (IQR)	19 (10–30)	16 (7–21)	20 (10–30)
Cost per patient, $, median (IQR)	6500 (3400–10,200)	5300 (2400–7200)	6800 (3400–10,200)
Total cohort cost, $ (%)	1,489,900 (93)	115,700 (7)	1,605,600 (100)
Summary of all healthcare utilization			
Patients using service[b], no. (%)	376 (46)	192 (25)	462 (55)
No. of admissions, median (IQR)	1 (1–2)	1 (1–2)	2 (1–3)
Length of stay[c], days, median (IQR)	20 (7–51)	8 (4–20)	19 (7–47)
Cost per patient, $, median (IQR)	11,100 (5100–32,100)	15,800 (7800–31,700)	16,800 (6200–41,300)
Total cohort cost, $ (%)	11,933,200 (66)	6,211,900 (34)	18,145,100 (100)

Costs reported in 2014 US dollars. Mean (standard deviation) of healthcare cost data are provided in eTable 3

no. number, *IQR* interquartile range

[a] Sample size indicates number of patients eligible for follow-up with any healthcare utilization data for each time period. During follow-up, $n = 815$ and $n = 764$ patients reported healthcare utilization data at 6- and 12-month follow-up, respectively, with a total of 839 patients ever reporting any healthcare utilization data during the entire 1-year follow-up period

[b] Percentages calculated by number of patients utilizing service divided by sample size in each follow-up time period

[c] Reported admissions with missing length of stay data (23 of 634 (3.6%) admissions) had length of stay imputed using the cohort median for each admission type (hospitalization, skilled nursing, or rehabilitation) and admission category (for hospitalization only). The length of stay is described as the median number of days per patient within each follow-up time period. The total length of stay represents the median total number of days over 12-month follow-up period

(3–20) hospital days, with estimated median (IQR) hospital cost of $18,756 ($7852–46,174). Few baseline factors were associated with increased healthcare utilization or cost. Out of 16 baseline variables evaluated, only cardiovascular comorbidity and ICU LOS were associated with increased hospitalizations, and sepsis as a risk factor for ARDS was associated with higher hospital costs. Importantly, patients' physical function and QOL at the 6-month assessment were associated with both hospitalization and hospital costs in the subsequent 6-month period.

Our study, the largest prospective, 1-year follow-up study of ARDS survivors' healthcare utilization to-date, supports the findings of prior smaller studies, including a prior multicenter ARDSNet study evaluating pulmonary artery catheter use [8], that healthcare utilization is high in the year after ARDS, with over one-third of patients hospitalized. Our finding that 10% of patients were readmitted within 30 days is consistent with prior studies focused on sepsis and general ICU survivors, which report 10–26% rehospitalization rates within 30 days [29, 35–38]. While our study demonstrated that higher estimated household income was independently associated with 30-day readmission, prior findings have been mixed regarding this issue [35, 39]. Heterogeneity in patient populations and international differences in healthcare systems may limit the comparability of these results.

Our study demonstrated that ICU LOS was associated with hospital readmission, in contrast to a multicenter Canadian study of patients receiving at least 7 days of mechanical ventilation, which demonstrated that ICU LOS was associated with ICU readmission, but not associated with hospital readmission [40]. This contrast may

Table 3 Longitudinal evaluation of baseline exposures' association with follow-up hospitalizations and associated costs after acute respiratory distress syndrome over 12 months

Variables	Any hospitalization[a]		Hospitalization costs	
	Odds ratio (95% CI)	p^b	Relative median (95% CI)	
Baseline patient data				
Age, per 10 years	1.04 (0.93, 1.16)	0.471	0.95 (0.85, 1.07)	0.423
Female	1.06 (0.79, 1.41)	0.706	1.28 (0.98, 1.67)	0.065
White	1.07 (0.74, 1.56)	0.707	0.83 (0.58, 1.19)	0.312
Estimated income[d], per $10,000	0.99 (0.94, 1.05)	0.772	1.04 (0.97, 1.11)	0.307
Healthcare insurance				
Private insurance	Ref	Ref	Ref	Ref
Medicare	1.19 (0.85, 1.67)	0.319	0.98 (0.69, 1.40)	0.874
Medicaid	1.44 (0.94, 2.21)	0.095	1.04 (0.68, 1.58)	0.865
Medicare and medicaid	1.25 (0.69, 2.25)	0.465	1.57 (0.96, 2.59)	0.073
No insurance	0.72 (0.42, 1.22)	0.224	1.23 (0.76, 1.99)	0.397
Obesity[e]	0.76 (0.56, 1.02)	0.066	0.96 (0.73, 1.27)	0.773
Cardiovascular disease	**1.39 (1.00, 1.92)**	**0.049**	1.11 (0.82, 1.50)	0.483
Diabetes mellitus	1.33 (0.95, 1.86)	0.091	1.22 (0.89, 1.67)	0.213
Chronic pulmonary disease	1.31 (0.94, 1.81)	0.106	1.16 (0.80, 1.67)	0.440
Baseline ICU-related data				
APACHE III, per 20	0.97 (0.87, 1.09)	0.656	1.03 (0.93, 1.14)	0.591
Sepsis as a risk factor	0.86 (0.61, 1.21)	0.382	**1.60 (1.15, 2.22)**	**0.005**
Tracheostomy in ICU	1.12 (0.74, 1.71)	0.582	1.35 (0.93, 1.96)	0.117
ICU length of stay, per week	**1.10 (1.01, 1.19)**	**0.023**	0.97 (0.93, 1.01)	0.156
Follow-up (12 vs. 6-month)	0.95 (0.72, 1.26)	0.714	0.87 (0.68, 1.10)	0.243

CI confidence interval, *APACHE* Acute Physiology and Chronic Health Evaluation, *ICU* intensive care unit

Bold values represent statistical significance $P < 0.05$

[a] The most common hospital admission categories for readmissions were (eTable 1) infection 109 (16%), pneumonia 101 (15%), gastrointestinal 94 (14%), respiratory (excluding pneumonia) 85 (12%), and cardiovascular 54 (8%)

[b] *P* values were calculated using multivariable logistic regression analysis of patients with any versus no hospitalization

[c] *P* values were calculated using multivariable linear regression analysis of log-transformed admission care costs associated with hospitalization

[d] Estimated household income is based on zip code of residence

[e] Obesity is defined as body mass index (BMI) $\geq$30 kg/m^2

be due to differences in healthcare systems, including availability of ICU beds and ICU admission practices, between the USA and Canada.

One-year post-ARDS hospital costs [mean (SD) $43,200 ($72,400)] (eTable 3) were higher than reported for sepsis [mean (95% CI) $17,601 ($14,803, $20,398)] in a Canadian cohort [41], but less than 1-year costs after prolonged mechanical ventilation in a single-center American cohort [$64,372 ($102,402)] [42]. These post-ARDS hospital costs are substantially greater than costs for patients who were hospitalized (at least once) during a yearlong period for other common medical conditions [e.g., chronic obstructive pulmonary disease and congestive heart failure: $2457 ($6462) and $2744 ($19,050), respectively] [43]. (All cost comparisons are reported in 2014 US dollars.)

Few critical care studies have evaluated the impact of post-discharge patient status on subsequent hospitalizations. A single-center, 5-year longitudinal follow-up of ARDS survivors in Baltimore, Maryland (ICAP study) [9], demonstrated similar findings to our multicenter national study, including both increased rates of hospitalization and increased cost with worse physical function and poorer quality of life. However, in addition, this ARDSNet study found that worse depressive and anxiety symptoms were associated with increased hospitalization, in contrast to the ICAP study and another single-center study [29, 44]. These prior studies may have been underpowered to detect such an association. Given that physical therapy and psychiatric visits were the two most costly outpatient categories, it is important to further highlight that physical impairment and mental health are important post-ARDS issues.

Although a number of attempted novel interventions have been unable to improve ICU survivor outcomes, our data demonstrate that potentially modifiable post-ARDS measures, such as physical function, are associated with subsequent hospitalizations. Hence, further efforts to devise and

Table 4 Evaluation 6-month follow-up exposures' association with 6- to 12- month follow-up hospitalization and associated costs after acute respiratory distress syndrome

Variables from 6-month follow-up, individually added to base model[a]	Any hospitalization		Hospitalization costs	
	Odds ratio (95% CI)	p^b	Relative median (95% CI)	p^c
Functional status—Functional Performance Inventory[d]				
FPI total score, per 0.35 points	**0.81 (0.72, 0.90)**	**<0.001**	**0.83 (0.76, 0.90)**	**<0.001**
Physical exercise subscale, per 0.43 points	**0.74 (0.65, 0.84)**	**<0.001**	**0.86 (0.78, 0.94)**	**0.001**
Maintaining house subscale, per 0.45 points	**0.79 (0.71, 0.88)**	**<0.001**	**0.82 (0.75, 0.90)**	**<0.001**
Body care subscale, per 0.32 points	**0.88 (0.79, 0.98)**	**0.016**	**0.81 (0.73, 0.89)**	**<0.001**
Psychiatric symptoms				
HADS-depression subscale[e], per 1.5	**1.08 (1.01, 1.15)**	**0.016**	1.06 (0.99, 1.13)	0.080
Depression (binary variable)[f]	**1.65 (1.08, 2.53)**	**0.021**	1.42 (0.97, 2.07)	0.069
HADS-anxiety subscale[e], per 1.5	**1.07 (1.00, 1.14)**	**0.035**	1.04 (0.98, 1.11)	0.202
Anxiety (binary variable)[f]	1.26 (0.82, 1.92)	0.291	1.31 (0.88, 1.96)	0.179
IES-R score[d], per 0.4	1.09 (0.99, 1.20)	0.060	1.03 (0.95, 1.12)	0.490
PTSD (binary variable)[g]	1.34 (0.82, 2.18)	0.246	0.96 (0.63, 1.45)	0.839
Cognition—Mini-Mental Status Exam				
Score, per 0.9	0.92 (0.82, 1.04)	0.163	**0.93 (0.86, 0.99)**	**0.035**
Score ≤24	1.34 (0.79, 2.27)	0.283	1.40 (0.91, 2.16)	0.124
Quality of life (QOL)				
Equation 5D VAS[d], per 10	**0.83 (0.76, 0.91)**	**<0.001**	**0.91 (0.84, 0.98)**	**0.016**
Equation 5D utility score[e], per 0.07	**0.88 (0.83, 0.94)**	**<0.001**	**0.93 (0.87, 0.99)**	**0.024**
SF-36v2 PCS[e], per 5	**0.73 (0.66, 0.80)**	**<0.001**	**0.91 (0.83, 0.99)**	**0.032**
SF-36v2 MCS[e], per 5	0.93 (0.87, 1.00)	0.056	0.95 (0.88, 1.02)	0.171

Bold values represent statistical significance $P < 0.05$

[a] Each post-discharge 6-month exposure was added separately to a base model that adjusted for all the baseline exposures presented in Table 3, with the outcome variable being evaluated during the subsequent 6- to 12-month follow-up period

[b] *P* values were calculated using multivariable logistic regression analysis of patients with any versus no hospitalization during 6- to 12-month follow-up

[c] *P* values were calculated using multivariable linear regression analysis of log-transformed costs associated with hospitalization during 6- to 12-month follow-up

[d] FPI, IES-R score, MMSE, and EQ-5D VAS were scaled by one-half of the standard deviation within this study cohort to approximate a minimally important difference [28]

[e] HADS, EQ-5D-utility score, SF-36v2 PCS, and MCS were scaled by the reported minimally important difference

[f] Depression and anxiety symptoms defined by HADS scores >8

[g] PTSD defined by IES-R score >1.6

evaluate care models and interventions to improve post-ICU physical function may be important for improving both patient outcomes and post-ICU healthcare costs.

The strengths of this study include its relatively large size and its multicenter, national, prospective, longitudinal design, with a high cohort retention rate (92%) and detailed data on post-discharge patient status and healthcare utilization. However, this study has potential limitations. First, this study enrolled patients from ARDSNet RCTs that had exclusions for severe pre-existing disease and survivors had a mean age of 49 years old, which may limit generalizability of these findings to other ARDS and non-ARDS patients. In addition, the exclusion of patients with baseline poor cognitive function and homelessness may further impact generalizability to all critically ill patients. However, our findings on frequency of healthcare utilization were similar to a separate observational study of ARDS survivors with fewer exclusion criteria [9], thus helping support generalizability. Second, baseline measures of healthcare utilization, physical function, and psychiatric symptoms were not available to determine whether post-ARDS healthcare utilization and patient status differed from pre-ARDS status [3, 36]. However, a population-based ICU study in Scotland [3] and a study of severe sepsis [36] both found excess hospitalization in ICU survivors compared to general hospital populations. Third, healthcare utilization data were self-reported, potentially leading to an underestimate due to recall bias [45], and excluded data for patients who died prior to follow-up. Fourth, this observational study does not establish a cause and effect between exposures and outcomes; hence, it is possible that, for example, poor physical function, psychiatric symptoms, and hospitalization may be represent pre-existing problems that may not

be readily amenable to improvements leading to reduced healthcare utilization and costs. Fifth, actual healthcare costs were not available, but were estimated on the basis of published methods from a nationally representative database [32], and ICU-related costs during hospital readmissions were accounted for as part of mean total costs within each admission diagnosis category, likely underestimating such costs. Lastly, we did not adjust the *P* value threshold used for statistical significance to account for multiple comparisons and, therefore, these findings should be interpreted as hypothesis-generating.

Conclusion

This national, multicenter, longitudinal study of ARDS survivors found that 40% of patients reported at least one hospitalization during 12-month follow-up, with one-quarter of those patients readmitted within 30 days of hospital discharge. While few baseline factors were associated with increased healthcare utilization, better physical function and QOL status at 6-month follow-up were associated with both lower hospital admissions and healthcare costs over the subsequent 6-month follow-up period. Hence, future research focused on improving post-ARDS morbidity is warranted with an aim of both improving patient outcomes and reducing healthcare utilization.

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Compliance with ethical standards

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All authors declare that they have no conflict of interest to disclose.

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